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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/079,929	02/19/2002	Sabina Sperandio	P-BU 5149	6504

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EXAMINER	
GAMETT, DANIEL C	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/079,929	SPERANDIO ET AL.	
	Examiner	Art Unit	
	Daniel C. Gamett	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *1-3 and 7-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-6 and 11-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application, Amendments, and Claims

1. Claims 4-6 and 11-16 are under examination. This office action is responsive to Applicant's remarks filed on 06/13/2005.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Maintained - 35 USC § 112

3. Claims 4-6 and 11-16 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Applicant's arguments filed 06/13/2005 have been fully considered but they are not persuasive. The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described

in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. Each of these factors has been addressed on the record; the pertinent matters will be reiterated with reference to Applicant's remarks. The instant disclosure fails to meet the enablement requirement for the following reasons:

a. *The nature of the invention:* Claims 4-6 are drawn to a method of inhibiting paraptotic cell death in a cell comprising contacting said cell with an effective amount of JNK inhibitor SP600125. Claims 11-16 are drawn to methods of treating a condition associated with excessive cell death in vivo.

b. *The breadth of the claims:* There are no limitations on the cell recited in claim 4, whereas in claims 5 and 6, the inhibition of paraptotic death of said cell occurs in a mammal or specifically a human, respectively. In claims 11-16, the effective amounts of SP600125 inhibit paraptotic cell death in vivo.

c. *The state of the prior art and the predictability or lack thereof in the art:* At the time of invention, the term "paraptosis" was newly coined; the cytological and biochemical differences between paraptosis and apoptosis were only beginning to be appreciated. The two forms of programmed cell death can be stimulated by the same stimuli (specification p. 6 lines 3-5: "Receptors involved in mediating cell death may

activate either the paraptotic or apoptotic pathway, or may activate both pathways.") and can be inhibited by the same inhibitors (specification p. 6 lines 25-29: "inhibitors or neutralizing agents of the Jun N-terminal kinases (JNKs) ... block both the paraptotic and the apoptotic cell death pathways."). It was known that apoptosis may or may not require JNK activity in different situations, depending on the nature of the cell death signal (Sabapathy et al 1999, Curr Biol. 1999 Feb 11; 9(3):116-25) and it was not known whether paraptosis would be similarly variable. Under those circumstances, a skilled artisan can only tell by experimentation whether (a) paraptosis will occur and (b) SP600125 inhibits said paraptosis, in any particular system. With regard to *in vivo* use and the treatment of specific conditions, it is noted that several conditions wherein programmed cell death is purported to be "non-apoptotic" are contemplated (e.g. p.1, line 26-p.2 line 14; see also claims 13-16), but it remains unknown whether any of these instances of cell death represent paraptosis as defined by applicant and, most importantly, it remains unknown as to whether any of these processes are dependent upon JNK activity and so may be inhibited by SP600125.

d. *The amount of direction or guidance present and the presence or absence of working examples:* Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The evidence that SP 600125 can inhibit paraptosis in any cells is indirect, being based on the observation "antisense oligonucleotide constructs for JNKI or JNK2 were able to inhibit IGFIR-IC induced paraptosis in 293T cells" (on p.38, lines 9-14). Applicant has pointed out that specific details are given in this example, such as the effective concentrations of the

oligonucleotides. This information does not provide enablement for the use of SP600125 because oligonucleotides target the mRNA for JNK whereas the SP600125 targets the enzyme. At best, these asserted results merely provide a basis for a hypothetical prediction that SP600125 is capable of inhibiting paraptosis in a model system. With regard to *in vivo* use, the specification does not establish that paraptosis as defined by applicant is actually involved in any condition or, if so, the paraptotic program involved is dependent upon JNK activity and so may be inhibited by SP600125. The specification offers no guidance as to critical matters that would enable treatments, such as patient selection, dosage, and the unpredictability that is inherent in extrapolating from a cell culture model to a complex system such as a diseased mammal.

e. *The quantity of experimentation needed:* Applicant agues that it would require only routine, not undue, experimentation for a skilled artisan to use the examples provided in the specification to develop a general method of inhibiting paraptosis, as in claims 4-6 and to develop a method of treating a condition as in claims 11-16. In order to practice the invention, however, the skilled artisan would need to perform experimentation to first determine whether SP600125 is indeed capable of inhibiting paraptosis in the exemplified model system and determine such critical parameters as dosage and timing. Further experimentation would be needed to determine if SP600125 generally inhibits paraptosis in "a cell" stimulated to undergo paraptosis, as opposed to human 293T cells expressing IGFIR-IC. Then, the artisan would need to perform the extensive experimentation necessary to establish a connection between specific *in vivo* conditions, paraptosis, and JNK activity. This would establish *why* to attempt to use SP

600125 for treatments, not *how* to use it. The artisan could then begin to move from tissue culture models to *in vivo* treatments. Contrary to Applicant's assertion, all of this amounts to undue experimentation, not routine development. The courts have stated that patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be patentable. Tossing out the mere germ of an idea does not constitute an enabling disclosure. Reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. See *Genentech v. Novo Nordick A/S* (CAFC) 42 USPQ2d 1001 (1997).

Claim Rejections Maintained - 35 USC § 102

4. Rejections of Claims 4-6 and 11-16 under 35 U.S.C. 102(e) as being anticipated by Bennett *et al.*, US Patent Application publication number 20040072888, 15 Apr., 2004, and of claims 4 and 5 under 35 U.S.C. 102(a) as being anticipated by Bennett *et al*, Proc. Nat. Acad. Sci. (USA) vol.98, no.24, Nov. 20, 2001 are maintained. Applicant's joint arguments against these rejections have been fully considered but they are not persuasive. As stated in the prior office action, the two references teach that SP600125 inhibits JNK and inhibits cell death; publication number 20040072888 teaches the use of SP600125 for treatment of conditions, including human diseases, involving programmed cell death. The instant specification teaches that JNK activity may be critical for paraptosis, a form of programmed cell death that had not been described at the time of either of the Bennett *et al.* publications. So, of course the prior art references are silent with respect to the inhibition of paraptosis by SP600125, as indicated in Applicant's remarks. Since SP600125 was already known to inhibit JNK and inhibit

programmed cell death, Applicant's discovery represents an elucidation of a mechanism but does not, however, make SP600125 into a new compound and it does not make the use of SP600125 to prevent cell death or treat conditions associated with programmed cell death a novel method. Applicant's argument against both rejections is that the property of inhibiting paraptosis is not necessarily present in SP600125 at all times. This argument holds only for those instances where paraptosis is not occurring or the paraptotic program is not dependent on JNK activity, in which cases the claimed methods are not operative. The ability to inhibit JNK is necessarily present in SP600125 and therefore SP600125 inherently inhibits JNK-dependent pathways including apoptosis, paraptosis, or any other process that may subsequently be found to require JNK activity.

Claim Rejections Maintained - 35 USC § 103

5. Claims 6 and 11-16 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bennett *et al*, Proc. Nat. Acad. Sci. (USA) vol.98, no.24, Nov. 20, 2001 as applied to claims 4 and 5, and in further view of Braun *et al.*, Expert Opin Investig Drugs. 1999 Oct;8(10):1599-1610). It is noted that Applicant did not argue this rejection found in section 10 of the 12/13/2004 Office Action, presumably on the assumption that the argument against the application of Bennett *et al.* to claims 4 and 5, if persuasive, would prevail against this rejection as well. The rejection is maintained for reasons of record and in view of the maintained rejections of claims 4 and 5 under 35 U.S.C. 102(a), above.

Conclusion

6. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C Gamett, Ph.D., whose telephone number is 571 272 1853. The examiner can normally be reached on M-F, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571 272 0961. The fax phone number for the organization where this application or proceeding is assigned is 571 273 8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DCG
Art Unit 1647
31 August 2005

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